# PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

## (PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>TX/4-33714A | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2005/003663 | International filing date *(day/month/year)*<br>07.04.2005 | Priority date *(day/month/year)*<br>08.04.2004 |
| International Patent Classification (IPC) or national classification and IPC<br>INV. A61K31/404 A61P11/06 A61P17/06 A61P19/02 A61P21/04 A61P37/06 | | |
| Applicant<br>NOVARTIS AG | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 30.01.2006 | 07.08.2006 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Borst, M<br>Telephone No. +49 89 2399-8648 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/003663

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-15 as originally filed

   **Claims, Numbers**

   1-6 filed with telefax on 23.01.2006

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6

because:

☒ the said international application, or the said claims Nos. 6 (no examination as to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1,3-6 |
| | No: | Claims | 2 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-6 |
| Industrial applicability (IA) | Yes: | Claims | 1-5 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

**Subject-matter excluded from international preliminary examination (Rule 67.1(iv) PCT)**

Claim 6 is directed to a method for the treatment of the human or animal body by therapy and, thus, relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated under Section V with respect to industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

## Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1: US-A-5 545 636 (HEATH, JR. ET AL) 13 August 1996 (1996-08-13) cited in the application

D2: BRADSHAW D ET AL: "THERAPEUTIC POTENTIAL OF PROTEIN KINASE C INHIBITORS" AGENTS AND ACTIONS, BIRKHAEUSER VERLAG, BASEL, CH, vol. 38, 1993, pages 135-147, XP009034964 ISSN: 0065-4299

D3: NIXON J S ET AL: "Novel, potent and selctive inhibitors of protein kinase C show oral anti-inflammatory activity" DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, BIOSCIENCE EDIPRINT INC, vol. 17, no. 8, 1991, pages 389-393, XP002111051 ISSN: 0378-6501

D4: WO 03/082859 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; EVENOU, JEAN-PIERRE; VON MATT, PETE) 9 October 2003 (2003-10-09)

D5: WO 03/104222 A (JANSSEN PHARMACEUTICA N.V; ZHANG, HAN-CHENG; MARYANOFF, BRUCE, E; YE,) 18 December 2003 (2003-12-18)

D6: WO 98/11105 A (ASTRA AKTIEBOLAG; BERGSTRAND, HAAKAN; KARABELAS, KOSTAS; LEPISTOE, MAT) 19 March 1998 (1998-03-19)

D7: EP-A-0 470 490 (F. HOFFMANN-LA ROCHE AG) 12 February 1992 (1992-02-12)

D8: HARRIS W ET AL: "Recent developments in protein kinase C inhibitors" EXPERT OPINION ON THERAPEUTIC PATENTS 1997 UNITED KINGDOM, vol. 7, no. 1, 1997, pages 63-68, XP002337325 ISSN: 1354-3776

### 1. Novelty (Article 33(2) PCT)

1.1. The subject-matter of present claims 2 is not new in the light of D1.

D1 (example 49 and 52; column 57, line 1-6) discloses compounds A and B as well as pharmaceutical compositions comprising the same which are for use in medicine, and therewith anticipates the subject-matter of claim 2, which is directed to the **first** medical use such compositions. In case of claims directed to the first medical use characteristics of specific therapeutic indications are not distinctive over the prior art, since the protection conferred by said claims is the use in medicien in general.

1.2. By restricting claims 1, 3-6 to compounds A and B in combination with particular therapeutic indications or with particular second agents novelty has been established for said claims over the prior art available.
In particular, D1 does not disclose the specific therapeutic indications nor the combination with a specific second agent as defined in the claims.

## 2. Inventive step (Article 33(3) PCT)

2.1. Being not new, the subject-matter of present claim 2 cannot be considered as inventive either.

2.2. The subject-matter of present claims 1-6 does not involve an inventive step.
Multiple prior art documents disclose the use of PKC inhibitors in general for the treatment of autoimmune diseases and of transplant rejection (cf. for instance: D2: page 135-138; figure 2; D3: abstract; D4: page 1 and 2; page 20; D5: page 10, line 5 - page 12, line 22; page 27, line 2 - page 28, line 17; page 36, line 17-22; D6: page3, line 7 - page 4, line 20; page 14, line 20-25 and D7: page 3, line 1-33; page 6, line 52 - page 7, line 6). The objective technical problem was to identify further PKC inhibitors for the same therapeutic indications.
It was known from D1 (example 49 and 52) that compounds according to formulae I-IV have PKC inhibitory activity and, therefore, obvious to use said compounds for solving the above technical problem. Moreover, the application fails to provide any ecidence showing that compounds A and B have therapeutic activity in the diseases claimed at all nor that the therapeutic activity thereof in the treatment of said diseases is improved vis-à-vis other PKC inhibitors, which would be a prerequisite for inventive step.

CLAIMS

1. Use of a protein kinase C inhibitor in the preparation of a pharmaceutical composition for the treatment and prevention of amyotrophic lateral sclerosis, multiple sclerosis and hepatitis C, for the treatment and prevention of organ or tissue transplant rejection and for the prevention of graft-versus-host disease, wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A pharmaceutical composition for use in the treatment and prevention of amyotrophic lateral sclerosis, multiple sclerosis, hepatitis C and/or organ or tissue transplant rejection and for the prevention of graft-versus-host disease, comprising a protein kinase C inhibitor together with one or more pharmaceutically acceptable diluents or carriers therefor, wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

3. A pharmaceutical combination comprising a) a protein kinase C inhibitor and b) at least one second agent selected from an immunosuppressant and immunomodulatory drug, wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

4. A combination according to claim 3 wherein the second agent is selected from a calcineurin inhibitor; an mTOR inhibitor, a rapalog, a corticosteroid, cyclophosphamide, azathioprene, methotrexate, an S1P receptor agonist, leflunomide or an analog thereof, mizoribine, mycophenolic acid or a salt thereof, mycophenolate mofetil, 15-deoxyspergualine or an analog thereof, an immunosuppressive monoclonal antibody, an immunomodulatory compound and an adhesion molecule inhibitor.

5. A combination according to claim 4 wherein the second agent is selected from cyclosporin A, FK506, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, FTY 720 or an analog thereof, mycophenolate sodium salt, an immunosuppressive monoclonal antibody to the leukocyte receptor MHC, CD2, CD3, CD4, CD 11a/CD18, CD7, CD25, CD27, B7, CD40, CD45, CD58, CD 137, ICOS, CD150 (SLAM), OX40, or 4-1BB or a

ligand thereof, LEA29Y, a LFA-1 antagonist, a selectin antagonist and a VLA-4 antagonist.

6. A method for treating or preventing amyotrophic lateral sclerosis, multiple sclerosis, hepatitis C, organ or tissue transplant rejection or for preventing graft-versus-host disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.